

The Efficiency of Telmisartan in Hypertension Management as a Monotherapy or Combined; Literature Review

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Abstract

Hypertension is considered a major health problem around the world. It's associated with increasing risk of mortality due to its complication which has a great impact on patient's life quality. Angiotensin Receptor Blocker has been widely used to manage hypertension, especially if diabetes coexists and the patient is less tolerable to angiotensin-converting enzyme inhibitors. In particular, telmisartan has been studied either as a monotherapy or combined with other antihypertensive agents. This study aims to understand the efficacy, safety, and tolerability of telmisartan as monotherapy or, in combination, is it superior to other agents? We used the PubMed database to search for relevant articles on the topic. Telmisartan administration showed excellent 24-hour protection against elevated BP, particularly in the early morning BP surge, which is the most expected period where cardiovascular events or strokes occur. In patients resistant to monotherapy, the use of telmisartan combinations provides better BP control compared to other agents, especially in the triple combination, where the drug's side effects are significantly decreased.

Keywords: Hypertension, Angiotensin receptor blocker, Telmisartan, Hypertension management

INTRODUCTION

Chronic uncontrolled hypertension is a significant risk factor for cardiovascular mortality and morbidity, strokes, heart failure, and renal failure [1-3]. Despite these recognized overwhelming complications, blood pressure is poorly controlled worldwide [3], and accounting for 34% in the United States [4] to 6% in other countries [5]. The poorly controlled hypertension can differ greatly among different countries, but it was thought to be related to drug preference along with their pharmacodynamics and their duration of action [3]. All of those mentioned above might play a significant role in controlling hypertension and prevent severe complications if the antihypertensive medication is chosen wisely [3]. Angiotensin Receptor Blocker (ARB) is commonly used for the treatment of hypertension, heart failure, coronary artery disease, diabetes, and chronic kidney disease (CKD) [6]. ARB acts on the renin-angiotensin-aldosterone system by the nonselective inhibition of angiotensin receptors that are proven effective on angiotensin II through the Angiotensin II type 2 (AT2) receptor may lead to incremental vasodilation and antiproliferative activity [6]. Unlike Angiotensin-Converting Enzyme (ACE) inhibitor, which acts mainly by blocking AT1 receptor only, ARB acts

by blocking AT1 and AT2 together, which may also trigger vasodilatation natriuresis [6].

Telmisartan is an oral, highly effective ARB with overall good tolerability [7]. Additionally, it has specific pharmacokinetic properties regarding the duration of action, which makes the ability of telmisartan to cover 24-hour protection in a once-daily dose [7, 8]. The efficiency of telmisartan in covering 24-hour controlling blood pressure has been found more significant than other ARBs, including

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How to cite this article: Alghamdi SA, Aldahneen MS, Beitar FS, Dyab NA, Afaneh LK, Almutairi RO, et al. The Efficiency of Telmisartan in Hypertension Management as a Monotherapy or Combined; Literature Review. Arch Pharm Pract. 2021;12(1):126-9. <https://doi.org/10.51847/NqVySmCa4j>

losartan, along with other agents, such as amlodipine and calcium channel blocker (CCB) [7]. Moreover, telmisartan resulted in a significantly greater mean of systolic blood pressure (SBP) and diastolic blood pressure (DBP) reduction during the last 6 hours before dosing, compared with losartan and amlodipine separately [7]. Besides, telmisartan is absorbed and distributed fastly to the peak plasma level compared to other ARBs, including losartan, candesartan, and valsartan [8]. Additionally, telmisartan binds to the AT1 receptor with high affinity [8].

RESULTS AND DISCUSSION

The Cardioprotective Effect of Telmisartan

Numerous experimental studies and clinical evidence have reported that the RAAS plays a major role in the pathophysiology of various cardiovascular diseases, for instance, myocardial infarction, stroke, and congestive heart failure [9]. Furthermore, the humoral system plays a significant role in the evolving and progression of hypertension and related end-organ damage [9]. Therefore, the pharmacokinetics of telmisartan allows to antagonize the adverse effects of early morning blood pressure rise and prevent cardiovascular events consequently [9]. The cardiovascular protection of telmisartan is not only limited to the control of blood pressure but also in preventing the progression of the structural and functional alterations of the cardiovascular and metabolic profile [10]. Moreover, telmisartan helps improve sympathetic modulation of the heart and homeostatic cardiovascular control, which may explain how the cardioprotective effect of telmisartan, especially in the early morning period, is characterized by an adrenergically-mediated sudden BP rise [9]. Finally, the protective mechanism of telmisartan on sympathetic/parasympathetic balance allows it to be advantageous in the glycemic metabolic profile [9].

Telmisartan as a Monotherapy

In a study comparing telmisartan to other types of ARBs, it found that its efficacy in covering 24-hour and allows to antagonize the adverse outcome of early morning BP increase on cardiovascular diseases [9]. The early morning BP rise and mean BP monitors are directly associated with target-organ damage and cardiovascular risk [11]. Epidemiologically, the incidence of acute myocardial infarction and ischemic strokes are highest in the initial 3-4 hours after arousal [11]. In two identically designed multinational, randomized, double-blind studies, once-daily administration of 80mg telmisartan decreased SBP and DBP throughout 24-hour, especially during the last 6-hour of the dosing interval [11]. The study compared 80mg of telmisartan to 160mg valsartan in mild-moderate hypertensive patients recorded by ambulatory blood pressure monitoring (ABPM) [11].

Similarly, telmisartan is reported to have significantly reduced mean ambulatory BP in the last 4-6 hours of the dosing interval compared to valsartan, losartan, or amlodipine

[11]. Besides, telmisartan offers better 48h protection for uncontrolled BP resulting in a missed dose than valsartan, which reassures patients who occasionally miss their dose [11]. Likewise, Joel *et al.* concluded in their trial that telmisartan provided 24-hour protection against elevated BP than losartan and valsartan [12]. Particularly the sustained BP control at the end of the dosing period [12].

While patients compliance is usually achieved with once-daily dosing, telmisartan provides a convenient option in the early morning and good coverage throughout the day, even in a missed dose [11, 12]. On the other hand, when telmisartan efficacy compared to ramipril in patients with vascular or high-risk diabetes but not heart failure, telmisartan found equally effective to ramipril and with decrease incidence of angioedema [13]. However, Zhenfeng Zheng *et al.* [14] found that telmisartan is without beneficial effect on BP when used as a monotherapy.

Telmisartan as a Combination Therapy

The combination treatment for controlling hypertension has been increasingly recognized. More than 70% of hypertensive adult patients will eventually need at least two antihypertensive medications, whether in combination therapy from the start or in addition to other medications [14, 15]. A patient without BP control is indicated for titration of the dose or adding a new antihypertensive agent [14, 15]. Nonetheless, adding a new agent before titration of the dose resulted in a more significant reduction in blood pressure [14, 15].

The American Society of Hypertension recommended a RAS inhibitor with either CCB or a diuretic in a single-pill combination (SPC) [16]. Initiate an early SPCs of antihypertensive agents, particularly telmisartan/amlodipine (T/A) and telmisartan/hydrochlorothiazide (T/H), was investigated by Julian Segura [16]. SPCs of telmisartan or hydrochlorothiazide have greater efficiency than monotherapy in all stages of hypertension [16]. Importantly, SPCs use resulted in fewer adverse effects, such as edema and hypokalemia, compared with amlodipine and hydrochlorothiazide monotherapy [16, 17].

Similarly, an SPC of telmisartan and amlodipine, including all doses, provides superior BP reduction than other antihypertensive agents alone and demonstrates 24-hour BP control [17]. Indeed, telmisartan plus amlodipine might be a reasonable choice for hypertensive patients who likely will require more than one agent for BP control [17]. Furthermore, the use of SPC offers better patient adherence in comparison to a separate agent [17]. In comparing different ARB's combinations with telmisartan, a prospective, randomized, blinded multicenter trial comparing telmisartan plus hydrochlorothiazide with valsartan plus hydrochlorothiazide (V/HCTZ) [18]. The study conclusively targeted obese, hypertensive patients with type-2 diabetes mellitus with a high risk for cardiovascular or stroke events [18]. A once-

daily dose of T/HCTZ was significantly superior to V/HCTZ during the last 6 hours of the 24-hour dosing interval, which the peak period for cardiovascular events [18]. In regards to the safety, apart from dizziness, which occurred in 3.3% of T/HCTZ-randomized patients compared to 0.2% in the V/HCTZ-randomized group, there were no differences in specific adverse effects between the two groups [18].

The Effect of Triple Combination Including Telmisartan

Regarding the triple combinations, The European Society of Cardiology recommends starting a low-dose combination therapy before single-dose therapy of hypertension [19]. Moreover, the British Hypertension Society and the National Clinical Guideline Center guidelines recommend 3-drug combinations of an ACE inhibitor or ARB, CCB, and a thiazide diuretic in case of 2-drug combination fails to control BP [19]. The efficacy and tolerability with the combination of telmisartan, amlodipine, and hydrochlorothiazide (TAH) were studied and resulted in better BP control in Korean hypertensives who fails to respond adequately to telmisartan and amlodipine [19].

Micatrio, the combination of ARB (telmisartan), CCB (amlodipine), and HCTZ, was studied earlier in 2009, and prof of the fixed-dose combination provides a mean reduction in SBP and DBP of 38.5 mmHg [20]. Subsequently, further studies found that Micatrio is highly effective in lowering SBP and DBP than telmisartan and amlodipine combined [20]. Furthermore, a trial showed that adding HCTZ to telmisartan and amlodipine resulted in a significant reduction of 12.3/8.4 mmHg on office BP compared to telmisartan/amlodipine [20]. Finally, Maladkar *et al.* confirmed in their trial result that the TAH is significantly effective in achieving better BP control if poorly responds to dual therapy [21]. These patients reported better quality of life after adding the triple therapy [21].

CONCLUSION

Controlling hypertension is one of the major modifiable risk factors for cardiovascular events and stroke. More precisely, RAAS has a significant impact on the cardiovascular system. Telmisartan, either monotherapy or combined, showed more significant BP control and provided 24-hour protection against elevated BP, especially during initial arousal. Moreover, the addition of cardiovascular protection, well tolerability, and less adverse effects, particularly in combination, helps to reduce cardiovascular complications. Various trials are studying the efficacy and safety to initiate dual or triple combination might provide better BP control and tolerability. However, meta-analyses for the existence of clinical trials may answer this question.

ACKNOWLEDGMENTS: The authors are grateful to all support and guidance of Dr. Alghamdi Saeed Ali M¹

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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